Sphingolipids

Introduction

Sphingolipid metabolism is **probably not worth the effort**. The names are long, convoluted, and difficult to master. Sphingolipids are a category of **lysosomal storage diseases**, which is as useful as saying replication is one of the functions of the nucleus. Lysosomes break stuff down, degrade foreign particles, and take complex molecules down to their constituents. Lysosomes work differently in different cells. So lysosomal storage diseases as a category, naturally, has spawned **40 subcategories** based on the mechanism and the target molecules it degrades.

When **lysosomes don't work, stuff accumulates**. When stuff accumulates, **organs scar and die**. Almost all of the lysosomal storage diseases result in **intellectual disability** and **death within one year**. They are **unpreventable** (aside from genetic counseling), **untreatable**, and **irreversible**.

WHAT'S IN THE LYSOSOMES	DISEASE CATEGORY
Mucus and lipid	Mucolipidosis
Mucus and sugar	Mucopolysaccharadosis
Glycoprotein	Glycoprotein
Lipid and amino acids	Sphingolipidosis

Table 17.1: Futility of Lysosomal Storage Disorder Nomenclature
Not worth the squeeze, this table is included for completeness. However low yield, the name of the disease implies the lysosome dysfunction. Mucus = Muco, Lipid = Lipid, Glyco = Glycoprotein, Saccharide = Sugar, Sphingolipid = Lipid and Amino.

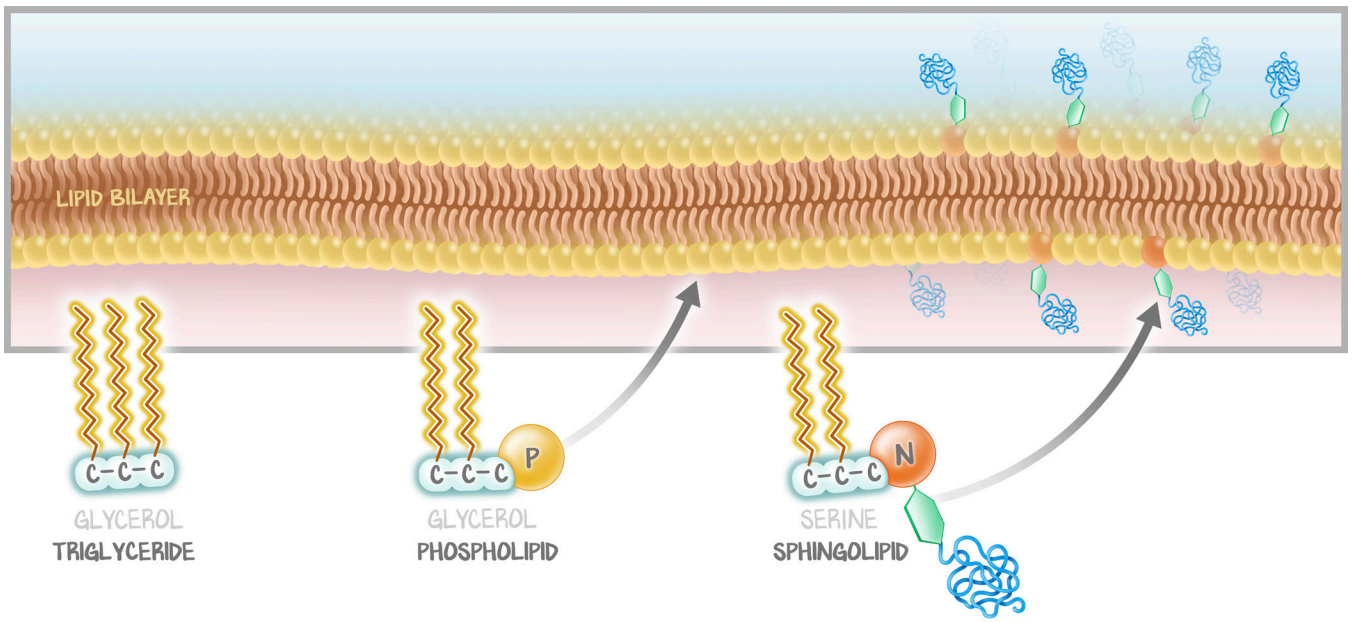

Figure 17.1: Triglycerides, Phospholipids, Sphingolipids
In concept, phospholipids are triglycerides with a polar phosphate group that replaces one of the fatty acids, and sphingolipids are a just more complicated polar head group. Technically, sphingolipids use serine, whereas phospholipids use glycerol.

But the Sphingolipids Have a Known Pathway…

…so you get to learn them. First, let's learn their similarities to lipids, to put their metabolism into perspective. Let's **first build** sphingolipids (any disease of synthesis is nonviable), then degrade them. Since they are degraded in lysosomes, it will be the **degradation pathways** that result in disease. But first we build. We build first so you understand the degradation—simply memorizing the names in the pathways will be counterproductive. It will stick better if you have perspective. We also color-code the diseases to correspond with the type of sphingolipid we are dealing with, a color-coding that makes sense only after we build them.

Let's go back to triglycerides. We were happy with the glycerol-backbone, with the addition of 3 fatty acid chains to make triglycerides to be stored. We touched on phospholipids, how there was a phosphate polar group instead of the third fatty acid. That meant there was a hydrophilic portion (position 3) and a hydrophobic portion (the two fatty-acid tails). And that was how we made the lipid bilayer of our cells.

Well, take **serine** (an amino acid) which **also has 3 carbons**, and start putting fatty acids on the 1 and 2 position, then add some polar compound on the 3-position…and sphingolipids start to form. The link is that serine, although being an amino acid, has three carbons, two of which will be fatty acid chains, and one of which will be a polar group. But where phospholipids stopped there, sphingolipids get extra stuff added to them. That extra stuff gives them their class. And that extra stuff, which should be degraded in a lysosome, gives rise to the lysosomal storage diseases.

Serine + **one fatty acid chain** is the backbone of all sphingolipids. This is called **sphingosine**. Take sphingosine (serine + one-fatty-acid) and **add another fatty acid** to get **ceramide**. Ceramide looks a lot like a phospholipid, except for one thing. It's an amino acid. An amino acid has nitrogen. And that means we can do more stuff to the 3-carbon backbone of serine than we could to the 3-carbon backbone of glycerol.

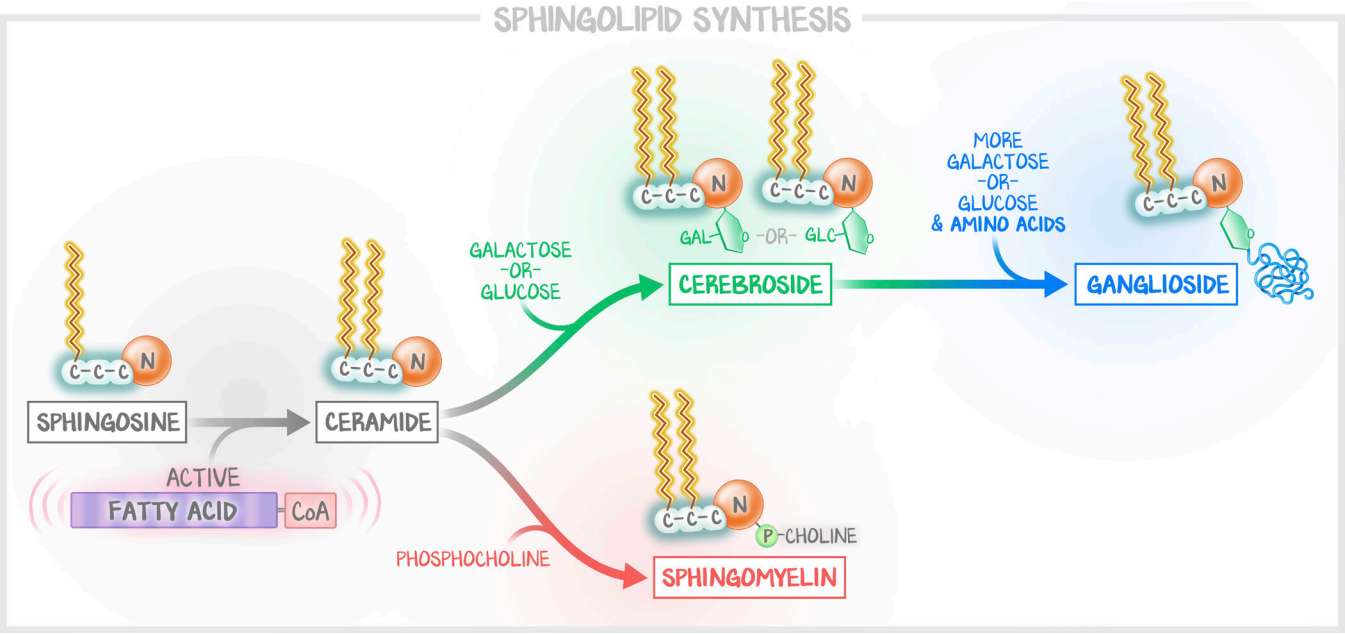

Figure 17.1: Sphingolipid Synthesis
Be cautious: this implies two synthesis trees—a sphingomyelin branch and a cerebroside to ganglioside branch. However, as we will see in Figure 17.3, "cerebroside" comes in the gal-cerebroside and glu-cerebroside forms.

Ceramide with an added **phosphocholine** is **sphingomyelin**. Sphingomyelin accumulation because of sphingomyelinase deficiency in lysosome causes accumulation of sphingomyelin (thank you for making that nomenclature so easy), to cause Niemann-Pick disease. Niemann-Pick begins with n, sphingomyelin ends in n.

Ceramide with an added **glucose** or **galactose** is a **cerebroside**. To cerebrosides, we can keep adding sugars, keep adding aminos such as **NANA** (basically, "amino + lots of carbon"), which will make them **gangliosides**.

Sphingomyelin, cerebroside, and ganglioside … those words sound like they might pertain to neural tissue. And sure enough, they do. But in such a vague and inconsistent manner that names reveal only that they were studied after devastating neurological effects and death in an inheritable pattern, not what they do or the symptoms they cause. At this point, **don't attempt to infer disease presentation** based on the name of the class. Now for the memorizing.

Degradation

The most complex sphingolipids will be built up, sugar on sugar, aminos and extras. They are taken apart in reverse of being built. **It just so happens** that there are three degradation pathways, **that do NOT correspond to the three types**. The types are shown by complexity of molecule and color-coded for memorization. The goal is to get to the common starting point, **ceramide**. From there, only serine and fatty acids remain. Given the severity of sphingolipid diseases, if the common pathway were defective (ceramide to sphingosine, sphingosine to constituents) the fetus would die.

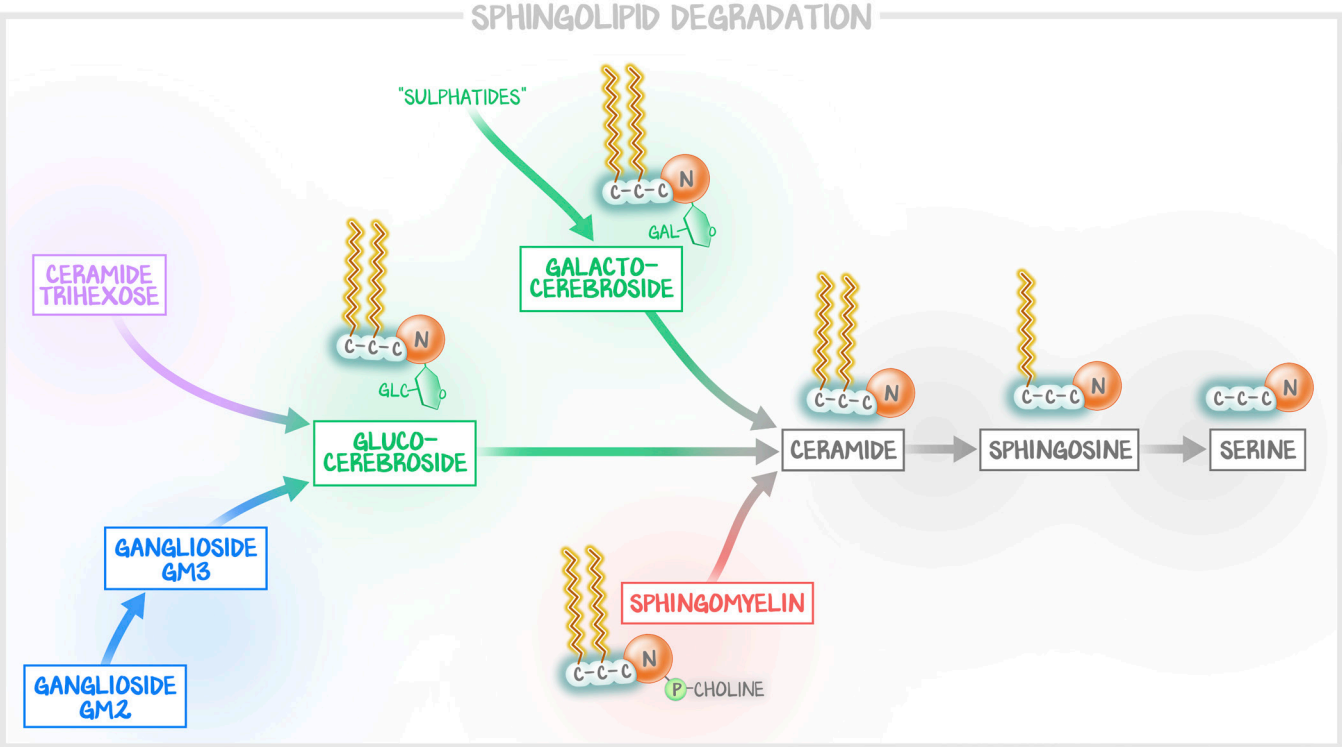

Figure 17.2: Sphingolipid Degradation
There are three main pathways to sphingolipid catabolism: the galactocerebroside, glucocerebroside, and sphingomyelin branches. This is how the video helps separate the disease states.

To get to ceramide, some degradations go through **gluco-cerebroside** (ceramide + a glucose). A defective **glucocerebrosidase** would render this pathway impossible, resulting in an **accumulation of glucocerebroside**, causing **Gaucher's disease**. This is an **autosomal recessive** genetic disorder that results in massive **hepatosplenomegaly** and problems with bones and joints. The pathognomonic finding is lysosomes filled with sugar, presenting as **PAS+ macrophages** that look like **wrinkled paper**.

To get to glucocerebroside, degredadation of complex **gangliosides** must occur. The pathway involving **ganglioside GM2** to GM3 uses the enzyme **hexose-amino-dase A** (hexosaminidase A), reminding us that gangliosides are a combination of both amino and sugar groups. This hexosaminidase A deficiency is **Tay-Sachs disease**, presenting in **Ashkenazi Jews** with **cherry-red macula**. There is **no organomegaly** (compare to Niemann-Pick). This is an **autosomal recessive** disorder.

Another ganglioside, **ceramide trihexose** (tri-hexose) must first have the 2nd and 3rd sugars removed to become gluco-ceberebroside. This is done by **α-galactosidase A** (which is frustrating because this has the word "galactosidase A" because it is a galactose remover, but it isn't the galactocerebrosidase that will follow below), a defect of which causes **ceramide trihexose accumulation** in lysosomes, giving **Fabry's disease**. Fabry's disease is special because it is the **only X-linked sphingolipid** disease. This causes the brain and nerves to go first: neurodegeneration and mental retardation, followed by cardiac and renal collapse.

To get to ceramide, some degradations go through **galactocerebroside** (ceramide + galactose). A defect of **galactocerebrosidase** is **Krabbe's** diseases, causing an accumulation of galacto-cerebroside in the lyososomes. **Autosomal recessive** inheritance, it causes **peripheral demylination**, mental retardation, and optic atrophy.

The sulfonated galactose groups called the "sulfatides" get that sulfur removed with **arylsulfatase A** in order to become galacto-cerebroside. A deficiency causes **metachromatic leukodystrophy**. This causes **central and peripheral demyelination** causing ataxia and dementia. Autosomal recessive.

Finally, **sphingomyelin** becomes ceramide under the influence of **sphingomyelinase**. A deficiency of sphingomyelinase causes an **accumulation of sphingomyelin**. This is, like the others, a progressive neurodegenerative disorder characterized by **cherry-red macula**, found in **Ashkenazi Jews**, is **autosomal recessive**, and will result in **organomegaly**. A biopsy reveals **zebra bodies**, also known as **lipid-laden macrophages**.

What to Know about Sphinigolipidosis

CLASS	NAMED	ENZYME	ACCUMULATION OF	PRESENTATION	GENES
Sphingo	**N**iemann-Pick	**Sphingomyelin**ase	**Sphingomyelin**	Cherry-red macula, organomegaly, intellectual disability, zebra bodies	AR
Gluco	Gaucher	**Glucocerebrosidase**	**Glucocerebroside**	Ashkenazi Jews, organomegaly, PAS-positive macrophages, wrinkled-paper macrophages, autosomal recessive	AR
Gluco	Tay-Sachs	Hexosaminidase A (sugar) + (protein)	**Ganglioside** GM2	Cherry-red macula, Ashkenazi Jews, intellectual disability	AR
Gluco	Fabry	α-Galactosidase A	Ceramide trihexose	Triad of peripheral neuropathy, angiokeratomas, and hypohidrosis, progresses to renal failure and cardiac failure	XR
Galacto	Krabbe	Galacto**cerebrosidase**	Galacto**cerebroside**	Central and peripheral demyelination, optic atrophy	AR
Galacto	MLD	Arylsulfatase A	**Cerebroside** sulfate	Central and peripheral demyelination with ataxia and dementia	AR

Table 17.2: Takeaways and Shortcuts for Sphingolipidosis (AR = Autosomal Recessive, XR = X-linked Recessive)
Memorize the chart, get the questions correct.